REMARKS

Reconsideration is requested.

Claims 1-19 are pending. Claims 7 and 11-13 have been withdrawn from consideration. The claims have been amended, without prejudice. New claims 14-19 find support throughout the specification as filed. New claims 14-18 are believed to read on the elected subject matter. No new matter has been added.

Claim 1 recites that the hydrophilic segment is linked via one of its ends to a single hydrophobic segment of formula I, or via each of its two ends to a hydrophobic segment of formula I, the two hydrophobic segments being the same or different. Support for that language can be found, for example, in paragraph [0015] of the Application, as published (US-2006-0182807-A1). Claim 1 recites that the claimed compound is for use as blood substitute or depolluting agent. Support for this language can be found throughout the specification as originally filed, for example, in the abstract. Claim 1 further recites "gas-associated form thereof." Support for this language can be found *inter alia* in original claim 1 (in the recitation of "the forms associated with a gas"), and in paragraph [0022] in the Application as published. Claim 1 also recites that "the sequenced block polymer is formulated as a particle whose core comprises the hydrophobic segment of formula I, and the oligosaccharide or polysaccharide hydrophilic segment lies at the surface of the particle." Such language finds support in the specification as filed, for example in original claim 8, paragraphs [0015], [0018] & [0020] and at lines 1-4 in paragraph [0026] of the published application. Claim 1 recites that "the hemoprotein associates with the oligosaccharide or polysaccharide hydrophilic

segment" finds support in lines 11-14 of paragraph [0026], and Examples 6 & 7 of the specification, as filed.

New claim 14 finds support in original claim 2. New claims 15 and 16 find support in original claim 6. New claims 17 and 18 find specific support in original claims 11 and 12. Claim 19 finds support throughout the specification and originally-filed claims. No new matter has been added.

Rejoinder and allowance of any claim defining a method of making and/or using a product defined by an allowable claim, at an appropriate time, are requested.

Rejoinder and examination of claim 13 and claim 19 with the other product claims is further requested.

The undersigned understands that an English translation of the foreign priority document is being prepared and will be forwarded under separate cover once received by the undersigned. The claims are believed to be supported by the priority document.

The Examiner is requested to confirm in a further communication that the figure filed April 28, 2005, is acceptable or advise the undersigned of any specific objection or rejection of the same.

The Section 102(a) rejection of claims 1-6 and 8-10 over Bourdon and Debuire, "Communiqué de presse, Prix de la valorization de la Recherche" June 25, 2002, XP0022276660 is obviated by the English translation of the priority document and/or the attached Rule 132 Declaration of Cédric Chauvierre. Reconsideration and withdrawal of the Section 102 rejection are requested.

The Section 103 rejection of claims 1-6 and 8-10 over Chauvierre (WO 02/39979) and Desai (U.S. Patent No. 6,096,331), is traversed. Reconsideration and

withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to believe that Chauvierre teaches nanoparticles comprising a block copolymer comprising a hydrophobic segment of formula I (*e.g.*, poly(alkylcyanoacrylate)) and a hydrophilic saccharide (*e.g.*, heparin). However, The Examiner appears to acknowledge that Chauvierre does not teach the use of heparin-coated poly(cyanoacrylate) nanoparticles for the delivery of hemoproteins such as hemoglobin.

The Examiner is further understood to believe that Desai allegedly discloses the synthesis of nanoparticles comprising synthetic block copolymers (citing column 10, lines 3-22), attached to biocompatible materials such as polysaccharides (citing column 9, lines 42-49). The Examiner appears to acknowledge that Desai does not disclose heparin as a contemplated polysaccharide. The Examiner is further understood to rely on Desai for an alleged suggestion that hemoglobin would be present in the polymeric shell (citing column 9 line 54 and column 11 line 63), and the Examiner is understood to conclude that Desai allegedly teaches a blood substitute.

The Examiner is further understood to believe that it would have been *prima facie* obvious for the ordinarily skilled artisan to modify the particles of Chauvierre to include the hemoglobin taught by Desai and that there was a reasonable expectation of success in the combination because Desai allegedly teaches that hemoglobin may be associated with the nanoparticle shell comprising a polysaccharide so as to be useful as a blood substitute.

Applicant respectfully disagrees with the conclusions set forth in the Office Action. Applicant respectfully submits that the combination of cited references does not support a *prima facie* case of obviousness for the reasons stated below.

The applicant believes that the legal standard for establishing a *prima facie* case of obviousness requires that three basic criteria be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success in the modification or in the combination; and (3) the prior art reference must teach all the claim limitations. All three requirements must be met to establish a *prima facie* case of obviousness. In addition, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (MPEP 706.02(j) (http://www.uspto.gov/web/offices/pac/mpep/documents/0700_706_02_j.htm#sect706.02j).

The cited combination of references fails *at least one* of the above three criteria, and therefore cannot be relied upon to establish a *prima facie* case of obviousness.

Applicant respectfully submits that the combination of cited references lacks the requisite motivation to establish a *prima facie* case of obviousness.

First, Applicant respectfully submits that the Examiner has mischaracterized the teachings of Desai. Specifically, Desai does not teach particles in the sense of the instant application. Instead, Desai is understood to teach *microcapsules* comprising a polymeric shell that encapsulates biologics of interest (*e.g.*, pharmaceutically active

agents), either in solution (see Desai, Example 2) or in solid form (see Desai, Example 6). The Applicant acknowledges that Desai uses the term "particle", or occasionally "nanoparticle." However, as evidenced throughout Desai, these terms refer to particles *encapsulating biologics*, where the shell forming the capsule is polymeric in nature. See, for example, Desai at column 9 lines 60-64.

> "Optionally, proteins such as a-2-macroglobulin, a known opsonin, could be used to enhance uptake of the shell encased particles of biologic by macrophase-like cells, or to enhance the uptake of the shell encased particles into the liver and spleen." [emphasis added]

The Examiner is further requested to see the following:

column 18 lines 24-26 ("... as the polymeric microcapsule is being formed ...")

column 18, lines 28-32 ("... with protein microcapsules prepared from a protein ...")

column 18, lines 43-45 ("... the encapsulated product ...")

column 19, lines 5-9 ("The encapsulation of DNA, RNA, plasmids ...")

column 19 lines 26-32 ("... by encapsulation into protein microcapsule shells ...")

column 19, lines 42-45, 57-60 and 63-64.

The applicant believes that Desai does not contemplate particles whose core comprises a hydrophobic polymeric segment covalently linked to one or both ends of an oligosaccharide or polysaccharide hydrophilic segment that lies at the surface of the particle, much less a hemoprotein associated with an oligosaccharide or polysaccharide segment coating these particles.

In fact, Desai does not contemplate, much less teach or suggest, sequenced block copolymers of any kind. Notably, Desai does not contemplate sequenced block

copolymers comprising an oligosaccharide or polysaccharide hydrophilic segment covalently attached via one (or two) of its ends to one (or two independent) hydrophobic polymer(s) in a sequenced fashion.

In addition, Desai does not teach or suggest hemoglobin associated with a particle shell comprising a polysaccharide. Desai does not contemplate hemoglobin associated with a polymeric particle (or nanoparticle). Rather, Desai teaches polymeric *microcapsules* where the polymeric material forming the shell of the capsule may be a protein, such as hemoglobin (See column 9, line 54), or a polysaccharide, such as dextran (See column 9, lines 45-46).

Furthermore, as the Examiner appears to acknowledge, Chauvierre does not teach the use of heparin-coated poly(cyanoacrylate) particles for the delivery of hemoproteins such as hemoglobin. There is no evidence or suggestion in Chauvierre or Desai, or in the general knowledge in the art at the time the invention was made, that hemoglobin, or hemoproteins in general, may associate with oligo- or polysaccharide-coated particles, while preserving its ability to reversibly bind ligands (*e.g.*, oxygen, carbon monoxide or nitric oxide gases).

The recognition that hemoglobin can associate with oligo- or polysaccharide-coated particles, while retaining its ability to reversibly bind ligands, was the Applicant's discovery. This recognition, as embodied in this Application, was later reported in 2004 by the inventors ((A) Chauvierre *et al.*, "Heparin coated poly(alkylcyanoacrylate) nanoparticles coupled to hemoglobin: a new oxygen carrier", Biomaterails, 2004, 25(15):3081-3086; (B) Chauvierre *et al.*, "A new generation of polymer nanoparticles for drug delivery", *Cellular and Molecular Biology*, 2004, 50(3), 233-239). See the full

documents, and for example, pages 3083-3085 of document A and pages 234-238 of document B. For the convenience of the Examiner, a copy of these references will be filed under separate cover.

The challenge of designing hemoglobin-based blood substitutes or gas depolluting agents is well recognized in the art. Indeed, for hemoglobin-associated particles to function as a blood substitute or gas depolluting agent, (i) the particles must have sufficient blood circulation life time, and (ii) the hemoglobin associated with the particles must retain its "functional" allosteric form, and its reversible ligand-binding ability. The Applicant was the first to reduce to practice sequenced block copolymer-based particles associated with a hemoprotein, exhibiting both these properties. See, for example, Example 9 in the present Application, Figure 3 in the aforementioned Document A, and Figure 4 of the document B mentioned above.

Thus, one of ordinary skill in the art, reading the cited references, would not have been motivated to modify the teachings of Chauvierre to associate the hemoglobin taught by Desai, to achieve the claimed subject matter.

The use of hemoglobin-associated saccharide-coated particles as blood substitutes or depolluting agents would not have been possible without Applicant's recognition that hemoglobin can in fact associate with oligo- or polysaccharide-coated particles while retaining its ability to reversibly bind ligands. Because Applicant's discovery was not known to the person of ordinary skill in the art before the present invention was made, there could not have been any motivation for the skilled practitioner to modify the teachings of Chauvierre to incorporate the hemoglobin taught

in Desai to design hemoglobin-associated oligo- or polysaccharide-coated particles for use as blood substitute or depolluting agent.

Moreover, the microcapsules of Desai lack the primary attribute necessary for use as a blood substitute or depolluting agent; namely, a long circulating half-life in the blood stream. Desai's microcapsules are designed to localize in certain tissues after administration. See, for example, column 6 lines 46-56 and paragraph bridging columns 6 and 7. Clearly, the object of Desai's teachings is to provide microcapsules that accumulate in certain tissues for localized therapeutic applications (See column 8 lines 61-64). In contrast, the block copolymer particles described in Chauvierre are designed to prevent their uptake by the organism's nonspecific immune defense system, and as a result, to increase their circulation in the blood stream. See, for example, lines 24-30 on page 1 of Chauvierre, an English translation of which is provided below by the applicant:

> "Moreover, these particles have the disadvantage of being rapidly uptaken by the macrophages of the Mononuclear Phagocyte System (MPS). Their lifetime *in vivo* is therefore reduced.
>
> The present invention specifically aims at overcoming the disadvantages referred to above, and proposes a new particle material whose polymeric structure derives from the association of a polymer similar to poly(alkylcyanoacrylate), with a segment of poly- or oligo-saccharide nature, such as dextran for example."

Accordingly, in contrast to Desai's microcapsules, the particles of Chauvierre are designed to avoid accumulation in organs of the mononuclear phagocyte system, including the liver and the spleen. Thus, one of ordinary skill in the art would not have been motivated to combine the teachings of Desai with those of Chauvierre because the

cited references have mutually exclusive goals/applications, and therefore combination of the teachings of one with the other, as the Examiner suggests, would have rendered the invention of Desai and/or Chauvierre inoperable.

In summary, the cited references do not provide the requisite motivation to make the presently claimed invention.

The combination of cited references fail to establish a *prima facie* case of obviousness because there was no motivation or suggestion in any of the cited references, or in the general knowledge in the art, to modify the teachings of Chauvierre and/or Desai to achieve the presently claimed subject matter. Accordingly, the Section 103 rejection should be withdrawn.

For completeness, the applicant further submits that there was no reasonable expectation of success within the cited references to make the claimed invention. The teachings, suggestion, and expectation of success must come from the prior art, not Applicant's disclosure. See *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicant respectfully submits that the cited combination of references provides no reasonable expectation of success.

As discussed above, prior to Applicant's invention, it was not known that oligo- or polysaccharide-coated particles were suitable as support for a hemoprotein, such as hemoglobin, whereby the hemoprotein retains its functional ability to reversibly bind and release ligands. The proposition of associating hemoglobin with the surface of a particle is counterintuitive, since it renders the hemoprotein vulnerable to the biological fluids to which it is exposed, and thus increases the risk of negatively impacting the hemoprotein's ability to reversibly bind and release ligands.

Desai does not enable the ordinarily skilled artisan to make microcapsules made up with a hemoglobin shell for use as blood substitute. Desai provides no teaching or working example of how this might be accomplished, nor any confirmatory tests establishing that the hemoglobin comprising the shell of the microcapsule has the ligand binding/releasing capability that is required to achieve its function as a blood substitute. Such is believed to have been required in light of prior art reporting failed attempts to design hemoglobin-associated constructs where hemoglobin's ability to bind and release ligands is preserved.

In contrast, as evidenced in Example 9 of the specification, Applicant has demonstrated that the hemoglobin associated with the oligosaccharide or polysaccharide hydrophilic segment coating the particle, as claimed, retains a reversible ligand-binding capacity, which is a property that is essential for its gas-transporter role (*i.e.*, property that is critical for the particle to be suitable for use as blood substitute or depolluting agent).

A person of ordinary skill in the art would not have been motivated to modify the particles of Chauvierre to associate the hemoglobin taught by Desai because there is no reasonable expectation of success that such association would result in particles suitable for use as blood substitute or depolluting agents (*i.e.*, where the reversible ligand-binding capacity of the associated hemoglobin is preserved). Therefore, the combination of cited references would not have made the claimed invention obvious.

Applicant respectfully submits that neither the Desai nor Chauvierre teaches or suggests a compound comprising a hemoprotein associated with a sequenced block copolymer formulated as a particle whose core comprises a hydrophobic segment of

formula I, and a oligosaccharide or polysaccharide hydrophilic segment laying at the surface of the particle; wherein the hemoprotein associates with the oligosaccharide or polysaccharide hydrophilic segment, as recited in pending claim 1. A necessary criterion for establishing a *prima facie* case of obviousness is understood to be that the prior art reference or references must teach or suggest all claim limitations. See Manual of Patent Examining Procedure, section 2143.03:

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re* Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). 'All words in a claim must be considered in judging the patentability of that claim against the prior art.' *In re* Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicant respectfully submits that Chauvierre does not teach the association of hemoglobin at the surface of oligo- or polysaccharide-coated particles. In addition, Desai does not teach particles in the sense of the instant application, instead it teaches microcapsules encapsulating a biologics of interest. Desai does not contemplate particles whose core comprises a hydrophobic polymeric segment covalently linked to one or both ends of an oligosaccharide or polysaccharide hydrophilic segment that lies at the surface of the particle, much less a hemoprotein associated with an oligosaccharide or polysaccharide segment coating the surface of these particles. Desai does not contemplate, much less teach or suggest, sequenced block copolymers of any kind. Finally, Desai does not teach nor suggest hemoglobin associated with a particle shell comprising a polysaccharide.

Thus, the cited references do not teach all the claim limitations.

Accordingly, there is nothing in the disclosure of the Chauvierre and Desai references that would have provided one of ordinary skill in the art motivation to make and use a compound for use as blood substitute or depolluting agent comprising a hemoprotein associated with a sequenced block copolymer formulated as a particle whose core comprises a hydrophobic segment of formula I, and a oligosaccharide or polysaccharide hydrophilic segment laying at the surface of the particle; wherein the hemoprotein associates with the oligosaccharide or polysaccharide hydrophilic segment.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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